CHAPTER 1

General introduction

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For a lot of people, because of the joy and happiness of a new life, pregnancy means being on cloud nine. However, the general population may not be aware that this does not apply to every woman. Psychopathology around pregnancy should not be underrated. For as many as 10-20% of all pregnant women, pregnancy results in black clouds, gathering over them.\textsuperscript{1,2}

This thesis will discuss different aspects of psychopathology around pregnancy. In the first part, consequences of anxiety and depression for the offspring as well as risk factors will be elucidated, using studies in the Netherlands and abroad. In the second part, effects of treatment of antenatal anxiety and depression using cognitive behavioural therapy on symptom level, perinatal outcomes, child development, and child behaviour when compared to care as usual will be assessed.

**Consequences of anxiety and depression**

Guilt, hopelessness, worthlessness, stress and excessive worries are examples of symptoms of anxiety and depression during or after pregnancy. Whether or not related to the pregnancy or the baby, these symptoms are associated with a range of adverse outcomes for mother and child. Parts of this thesis focus on their effects on breastfeeding and long-term effects on mental health in the offspring.

Symptoms of anxiety and depression not only cause uncomfortable feelings, but may also adversely affect the overall health of women.\textsuperscript{3} Anxiety and depression are associated with numerous diseases including coronary heart disease,\textsuperscript{4,5} diabetes mellitus,\textsuperscript{6,7} stroke,\textsuperscript{8,9} and even Parkinson's disease.\textsuperscript{10} A recent review demonstrated that the pooled relative risk of all-cause mortality among those with mental disorders was 2.22 and concluded that mental disorders, especially anxiety and depression, rank among the most substantial causes of death worldwide.\textsuperscript{11}

As for the child, long before birth, the adverse effects of the psychopathology of an antenatally anxious or depressed woman on her offspring may commence. Indeed, there is ample evidence that symptoms of anxiety and depression have adverse effects on perinatal outcomes\textsuperscript{12,13} and cognitive, motor and psychosocial development of the offspring.\textsuperscript{14-20} There are several theoretically possible mechanisms through which depression or anxiety during pregnancy could have an adverse effect on the offspring. These can be divided into direct and indirect.

A direct mechanism is one in which depression and/or anxiety activates the maternal stress system, leading to elevated glucocorticoid levels. Subsequently, this may influence the development and long-term physiology of the foetus' brain by passing the placenta. This direct mechanism is called “early life programming” or Barker's theory and is a hypothesis for the
(partial) explanation of brain disorders and cardiovascular disease in the offspring.\textsuperscript{21,22} In this theory, it is stated that maternal hormones and other substances influence the body and mind of a foetus in utero, and that the foetus’ body is adapted due to this influence. This adaptation is posed to be long-term.\textsuperscript{22} Furthermore, epigenetic variation(s) have been proposed as a mechanism in linking early life exposures to long-term psychological and behavioural outcomes.\textsuperscript{23}

The effect of maternal stress on the developing foetus may also be (partly) indirect. Women, suffering from antenatal anxiety and depression symptoms tend to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, increased drinking and smoking habits, neglecting prenatal care), which may influence the development of the foetus.\textsuperscript{24-27} Another indirect way in which antenatal anxiety and depression might influence the mental development of the offspring is when the antenatal psychopathology remains after delivery and turns into postnatal psychopathology. In this way, mother-child attachment might be endangered, because the mother has a reduced ability to respond to the child. Children from anxious and depressed mothers are breastfed for a shorter time\textsuperscript{28} and have a higher risk of insecure attachment, which in turn is associated with cognitive, behavioural and emotional problems.\textsuperscript{29-32} Finally, the association between antenatal psychopathology and adverse outcomes in the offspring might be indirect because this could be explained by a shared genetic or environmental predisposition between mother and child.

Whatever the actual mechanism(s) involved is/are, there is convincing evidence that children whose mothers suffered from anxiety or depression during pregnancy have an increased risk of behavioural, emotional and developmental problems.\textsuperscript{14-20} Additionally, when these symptoms are present during the postpartum period, women express more negative emotions and are less sensitively attuned to their children.\textsuperscript{33} This may have adverse effects on the child, e.g. attachment insecurity,\textsuperscript{34-37} delay in emotional development,\textsuperscript{37} social and interaction difficulties,\textsuperscript{38} and increased risk of developing violent behaviour.\textsuperscript{39} Although maternal postpartum depression is associated with mental health problems in childhood, it is largely unknown to what extent this association could be explained by parental psychopathology outside the postpartum period. Furthermore, there is debate whether the association is specific to the internalising or externalising domain of psychopathology and whether the effects extend into adolescence.\textsuperscript{37,40-44}

Whatever the case may be, at population level substantial total mental health gains may be accomplished when depressed or anxious women are adequately treated during their pregnancy, even if the effect size of the treatment is relatively small.
Early identification of risk factors

Parts of this thesis focus on risk factors for anxiety and depression during pregnancy. Identification of these risk factors may lead to identification of vulnerable groups of pregnant women, which eventually may lead to more effective targeting of prevention programmes and treatments. Risk factors include earlier (episodes of) psychopathology, unintended pregnancy, low social support, low socio-economic status (SES), and negative life events.\(^{45-47}\) This thesis will focus on a number of potential risk factors, of which a short description follows. More detailed descriptions of these and other risk factors follow later at a later stage in this thesis.

Negative life events

A well-known general risk factor for depression is the experience of a negative life event.\(^ {46,47}\) Indeed, negative life events experienced before pregnancy have shown to be a strong predictor of depression during pregnancy and possibly also anxiety.\(^ {46,47}\)

However, the relevance of the timing of events is still unclear.\(^ {46-48}\) Earlier research among adults from the general population showed that the association between negative life events and psychopathology is generally stronger when the life event happened more recently.\(^ {49,50}\) A different pattern is observed for childhood traumas of which the effects show substantial latency, i.e. they strongly link to an increased risk of psychopathology in adulthood.\(^ {51,52}\) Whether these time relationships generalize to pregnancy is, however, still unknown.

Socio-economic status

In both general population and in postpartum women, low socio-economic status (SES) has been associated with depression and anxiety.\(^ {53,54}\) Because antenatal and postnatal psychopathology are strongly correlated,\(^ {55}\) low SES may also be a risk factor for antenatal anxiety and depression.\(^ {47,48}\) Yet, the literature is still inconclusive about which aspects of SES, paternal and maternal, play a role.\(^ {46}\) Low SES and negative life events before pregnancy are not only associated with anxiety and depression during pregnancy, but may also have an adverse effect on birth weight and preterm birth which underlines the importance of their study.\(^ {56-58}\)

As low SES and negative life events are likely to be interrelated and because women with a low SES may have less mental resources and may be less able to cope with negative life events earlier in life, it may well be that these risk factors interact. Therefore, it can be hypothesised that women with a low SES are more vulnerable to the effects of negative life events on anxiety,
depression, and low birth weight or preterm birth compared to their peers with a normal or high SES. To date this is uncertain.

Even less is known about the prevalence and severity of anxiety and depression among pregnant women in the developing country Nicaragua. Depression and anxiety rates among pregnant women are less well known, but presumably higher. Indeed, it has been estimated that in developing countries, one in three to one in five pregnant women experiences a significant mental health problem, comparing to one in ten in developed countries.\(^5^9\) It is assumed that this high prevalence is the result of lower socio-economic development of the population, abuse, violence, and deficiency in mental health care.\(^5^9,6^0\) Nevertheless, to date the prevalence of depression and anxiety during pregnancy and their comorbidity are not known for the Central America region.

**Personality traits**

One of the earlier mentioned adverse effects of anxiety and depression around pregnancy, is that women who experience these symptoms breastfeed for a shorter period of time and are less likely to exclusively breastfeed.\(^2^8,6^1,6^2\) A recent study even showed that psychosocial factors are the strongest predictors of exclusive breastfeeding, i.e. receiving (expressed) breast milk only and, if necessary, drops and syrups like vitamins, minerals and medicines.\(^2^8,6^3\) Nevertheless, a recent review concluded that there is very limited research examining roles of psychosocial factors on six months exclusive breastfeeding.\(^6^4\)

A possibly important factor in relation to breastfeeding is personality, which can be described as individual differences in thoughts, feelings and behaviour. The well-known Five Factor Model, also known as ‘Big Five’, describes personality as consisting of five personality traits that describe individual differences between people.\(^6^5\) Each trait can be further divided into six facets, as presented in table 1.

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Although studies assessing relationships between personality and breastfeeding lacked methodological robustness, these showed positive associations of higher levels of agreeableness, extraversion, and openness with breastfeeding. Furthermore, in two recent large meta-analyses in general population, low consciousness, low extraversion, high neuroticism personality traits were associated with major depression and general anxiety disorder. Two studies among pregnant women showed that low agreeableness, low consciousness, and high neuroticism seem to be associated with symptoms of depression.

Because of these associations, breastfeeding outcomes may in part be explained by symptoms of anxiety or depression. However, this explanation has never been studied.

**Current treatment options**

Parts of this thesis focus on treatment of anxiety and depression during pregnancy. According to the current guidelines of the Dutch Association of Obstetrics & Gynaecology (Nederlandse Vereniging voor Obstetrie & Gynaecologie; NVOG), the British National Institute for Health and Care Excellence (NICE), the Australian Beyondblue, the American Psychiatric Association (APA), and the American College of Obstetricians and Gynecologists (ACOG), three treatment options for ante- and postnatal anxiety and depression should be considered: medication, psychotherapy, or a combination of both.

Due to ethical concerns, to date, no experimental research has been performed to prove the effects of anxiolytics and antidepressants during pregnancy. According to the guidelines, it is implausible that their effects with pregnant women differ from effects in the case of non-pregnant women. However, when using medicines as treatment, the advantages of decreasing the maternal symptoms should be equated to the disadvantages of the possible dose-dependent toxicity on the unborn foetus. Although there is a lot of clinical experience in using tricyclic antidepressants (TCAs), both in non-pregnant and in pregnant women, prudence is called for because these can cause neonatal withdrawal reactions. Monoamine-oxidase inhibitors (MAOIs) should be avoided during pregnancy because of the risk of a maternal hypertensive reaction. Additionally, there are reports of teratogenicity while using MAOIs. A commonly used group of antidepressants is formed by the serotonin-reuptake inhibitors (SSRIs). According to the guidelines, none of the types of SSRIs is clearly preferred during pregnancy, again due to absence of research. Nevertheless, Sertraline (Zoloft®, Lustral®) and Citalopram (Cipramil®, Celexa®) may have the lowest risk of adverse neonatal effects. Conversely, Paroxetine (Seroxat®, Paxil®) has been associated with low birth weight and congenital
abnormalities. Finally, Escitalopram (Lexapro®, Cipralex®) and Fluvoxamine (Fevarin®, Luvox®) have been less researched. When a woman uses SSRI's during pregnancy, both delivery in a hospital and neonatal observation under supervision of a paediatrician for a minimum of 12 hours after birth are recommended, because of the risk of neonatal persistent pulmonary hypertension. As in every medicinal therapy, the lowest possible dosage, still providing an effective result, should be prescribed, in pregnant as well as in breastfeeding women.

Likewise, the evidence of the effectivity of psychotherapy as treatment for psychopathology during pregnancy is insufficient. Nevertheless, women seem to have a preference for cognitive behavioural therapy over antidepressants. Cognitive behavioural therapy is one of the most often applied forms of psychotherapy and is based upon a combination of basic behavioural and cognitive principles. In the non-pregnant population, cognitive behavioural therapy has proven to be effective in many randomised controlled trials and it is implausible that its effects in pregnant women differ from effects in non-pregnant women. However, there is only mixed evidence of beneficial effects of cognitive behavioural therapy during pregnancy.

Literature provides only four randomised controlled trials that investigated the effect of cognitive behavioural therapy of antenataly provided cognitive behavioural therapy. Three studies assessed the effect of the therapy on anxiety or depressive symptoms during pregnancy. One showed a non-significant reduction in depression symptom level, another showed a significant reduction in depression symptom level, and only one assessed both depression and anxiety symptom levels. In the last study, no beneficial effects of cognitive behavioural therapy on symptom levels of anxiety or depression were shown. None of the four trials investigated perinatal effects and only one assessed effects on the offspring. The latter study showed no effect of antenatal cognitive behavioural therapy on offspring cognitive, socio-emotional, or physical development at age 7. Nevertheless, this study only assessed parent-reported child development, which may have been subject to reporting bias, and no offspring behavioural problems were assessed.

In conclusion, there is sparse evidence for the effectivity of cognitive behavioural therapy and adverse foetal effects cannot be precluded. While perinatal outcomes such as birth weight and gestational age at birth depend on many factors, psychopathology as well as its treatment may negatively affect them. Clearly, more evidence is needed to assess the effectiveness and possible perinatal ‘side effects’ of cognitive behavioural therapy during pregnancy.

In part II of this thesis, the effectiveness of a cognitive behavioural therapy intervention was investigated among pregnant women with subclinical...
symptoms of anxiety and depression. The therapy was designed especially for pregnant women with these symptoms and consisted of several optional modules with specific evidence-based cognitive behavioural therapy interventions. These focused on the treatment of anxiety disorders, depressive disorders, trauma and post-traumatic stress disorder. In addition, this treatment was targeted at identifying and challenging dysfunctional cognitions, schemata (i.e. cognitive frameworks that help to organise and interpret information) and exploring with the patient alternative coping styles. More detailed descriptions of the intervention as well as the study design follow later on in this thesis.

Studies in this thesis

In this thesis, data was used from multiple cohorts. Dutch data was derived from TRAILS, the PAD-study and the PROMISES-study. One of the chapters presents a explorative study in Nicaragua, where a small population-based study was performed.

TRAILS

The TRacking Adolescents’ Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch (pre)adolescents, with the aim to chart and explain the development of mental health from preadolescence into adulthood, both at the level of psychopathology and the levels of underlying vulnerability and environmental risk. Sample selection of children around twelve years of age from the general population attending participating schools concerned five municipalities in the North of the Netherlands. A parallel clinical cohort included children who have been referred at least once to the child psychiatric outpatient clinic of the University Medical Center Groningen at any point in their life. Measurements and procedures in TRAILS-CC were identical to those in the general population cohort. In TRAILS, 2230 children were included in the general population cohort, as well as 543 children in the clinical cohort.

PAD-study

The Pregnancy Anxiety and Depression (PAD)-study is a population-based observational prospective cohort study wherein psychological, medical and social factors during pregnancy and the postpartum period were investigated. Women in their first trimester of pregnancy were invited to participate when visiting one of the 109 participating midwifery practices or nine participating gynaecology and obstetrics departments throughout the Netherlands, or through advertisements in nation-wide media. Only women not mastering the Dutch language were excluded. Before entering the study,
women provided written informed consent, which includes the option to give permission to the researchers to derive medical birth records. Participants were asked to complete online questionnaires at inclusion (around 10-15 weeks of gestation), at 24 and 36 weeks of gestation and at 6 and 24 weeks after pregnancy. In the PAD-study, 8143 women were included.

PROMISES-study

The Pregnancy Outcomes after a Maternity Intervention for Stressful Emotions (PROMISES)-study is a randomised controlled single-blind trial that assesses the effects of cognitive behavioural therapy in 282 pregnant women, compared with care as usual. Participants of the PAD-study showing at least moderate symptoms of anxiety and/or depression were invited to participate in the PROMISES-study. Only women currently receiving psychotherapy, having a high suicidal risk, having a substantial physical disease, presenting with illegal substance abuse, or having a psychiatric disorder, psychoses or manic disorder, were excluded from participation in the PROMISES-study. In addition to the assessments of the PAD-study, the diagnostic SCID-I interview was administered, and participants were asked to complete online questionnaires at 12 and 18 months after pregnancy. Outcome measures included changes in the levels of anxiety and depressive symptoms of the women, perinatal outcomes as derived from medical birth records, and cognitive, fine and gross motoric development as well as child behaviour in the offspring as assessed at 18 months of age.

Nicaragua study

The Nicaragua study is a population-based cross-sectional study, which consisted of pregnant women who visited a public hospital or one of the two participating community health centres in the rural south of Nicaragua. During the inclusion period, all pregnant women were invited to participate in this study. When women were not able to read the questionnaire due to illiteracy, the researchers or nurses read the questionnaire aloud. We believed this was a better method than excluding all analphabetic women. The only women who were excluded from participation were women who had no oral mastery of the Spanish language. Before entering the study, women provided informed consent. Participants were asked to complete a questionnaire on symptoms of psychopathology and availability of professional psychological help. In the Nicaragua study, 98 women were included.

Detailed information about the design of and measurements within these studies are described further on in this thesis.
Outline and scope of this thesis

This thesis consists of two parts, of which the first consists of observational studies and the second of an intervention study. The observational studies are several analyses, based on the earlier mentioned TRAILS, PAD, and Nicaragua studies. The intervention study, PROMISES, is a randomised controlled trial designed to assess the effects of cognitive behavioural therapy during pregnancy on both mother and child, when compared to care as usual.

Part I: Observational studies

Chapter 2 describes the screening and treatment of two women with psychopathology during pregnancy. Although the patients experienced different complaints in different situations, the impact on woman, partner and child(ren) was in both cases tremendous. The cases make clear how relevant early screening and treatment of symptoms of anxiety and depression is during and after pregnancy.

Chapter 3 demonstrates the associations of the number of prior negative life events with symptoms of anxiety and depression early in pregnancy. Furthermore, we assessed which aspects of SES are associated with anxiety and depression. Finally, we investigated potential effect modification of the associations of the number of prior negative life events with symptoms of anxiety and depression by relevant aspects of SES. Additionally, we repeated these analyses on perinatal outcomes.

Chapter 4 presents our explorative study to investigate the prevalence and severity of anxiety and depression during pregnancy in the Central American developing country Nicaragua, as well as the availability of mental health care. We compared our Central-American findings to the findings of the PAD-study in the Netherlands.

Chapter 5 describes the possible independent associations of the big five personality traits and symptom levels of anxiety and depression with meeting the World Health Organisation (WHO)-recommendation of six months exclusive breastfeeding.

Chapter 6 demonstrates the associations of postpartum depression with internalising and externalising mental health problems in the offspring during adolescence. We investigated whether the associations were independent of parental lifetime psychopathology, to gain insight into a potential direct effect of postpartum depression.
Part II: Randomised controlled trial

**Chapter 7** presents the design of the PROMISES-study. This chapter is based on the published protocol and a book chapter. Additionally, the screening of participants in the PAD-study for eligibility for participation in the PROMISES-study is described.

**Chapter 8** reports the effects of cognitive behavioural therapy on the level of anxiety and depressive symptoms at 36 weeks of gestation, as compared to care as usual. We assumed additional reduction in symptom levels in participants who received cognitive behavioural therapy than in participants who received care as usual.

**Chapter 9** describes the effects of cognitive behavioural therapy on perinatal outcomes including birth weight and gestational age at birth, as compared to care as usual. We hypothesised that perinatal outcomes were better in participants who received cognitive behavioural therapy than in participants who received care as usual.

**Chapter 10** is a preliminary report on the effects of cognitive behavioural therapy on child outcomes at 18 months, as compared to care as usual. We assessed cognitive, fine and gross motoric development as well as child behaviour, as a predictor for psychological problems later in life. We assumed that both child development and child behaviour were more optimal in offspring of participants who received cognitive behavioural therapy than in offspring of participants who received care as usual.

**Chapter 11** provides the general discussion of the thesis and gives recommendations for clinical practice and for future research.

The thesis ends with a summary in English as well as in Dutch.
PART I

Observational studies